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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,144	MASUDA, ESTEBAN	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/20/06, 11/02/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Upon further consideration, the requirement for restriction between the cyclic peptides of claims 45-52 and the screening methods of claims 53-58 is withdrawn because the search of both groups does not present a significant burden. In addition, the election of species requirement is withdrawn because the search of all claimed species does not present a significant burden.

The restriction requirement as set forth in the Office actions mailed on 02/26/2008 and 10/16/2008 are hereby withdrawn. In view of the withdrawal of the restriction requirement, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Information Disclosure Statement

2. The information disclosure statement filed 12/20/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Specifically, copies of non-patent literature references Kinsella *et al.* and Nutt *et al.* have not been provided; only the abstracts have been submitted. The IDS should be amended to indicate that only the abstract is submitted or the full article

should be submitted. In addition, the citation for Nutt *et al.* is missing the journal or book title, volume, issue number and pages.

Sequence Compliance

3. This application is objected to because the amino acid and nucleic acid sequences in Figure 7 are not associated with sequence identifiers. All sequences longer than ten nucleotides or four amino acids referenced in the specification must include a sequence identifier. See MPEP § 2421-2422. Because the sequences are included in the sequence listing, the specification should be amended to include the appropriate sequence identifiers in the figure legend of Figure 7 or in the figure directly.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 45-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include: 1) the scope of the invention; 2) actual reduction to practice; 3) disclosure of drawings or structural chemical formulas; 4) relevant identifying characteristics including complete structure, partial structure, physical and/or chemical properties, and structure/function

correlation; 5) method of making the claimed compounds; 6) level of skill and knowledge in the art; and 7) predictability in the art.

Scope of the Invention

The claims are drawn to cyclic peptide comprising 1) a chaperone binding region and 2) a target binding region of wholly or partially unknown sequence. The USPTO gives claims their broadest reasonable interpretation in light of the specification.

The instant specification defines the term "chaperone" as "any molecule or protein capable of 'presenting' a cyclic peptide to another molecule. Thus, 'chaperones' are intended to include those proteins commonly known in the art as chaperones, as well as any other proteins or molecules capable of binding a candidate cyclic peptide and presenting it to another molecule, as described herein." (paragraph 0030) In light of this definition, the scope of chaperone binding region includes any peptide sequence that is capable of binding to any other protein or molecule. Claim 45 limits the scope of the chaperone to intracellular polypeptides, and therefore the scope of the chaperone binding region to any peptide that is capable of binding to any intracellular polypeptide. The specification states that the complex formed by the cyclic peptide and protein or molecular partner functions to present the cyclic peptide to another model. The term "present" is not defined in the specification. The Merriam-Webster online dictionary defines "present" as "to aim, point, or direct; to offer to view." Broadest reasonable interpretation of the term "present" in the context of the instant claims is not limited to resulting in the binding of the chaperone-cyclic peptide complex to a target but rather includes the potential to form such a complex. That is, binding of the cyclic peptide to the chaperone satisfies the requirement that the cyclic peptide is presented because the part of the cyclic peptide not directly involved in the

chaperone-peptide interface would be available to other intracellular proteins or molecules. In summary, broadest reasonable interpretation of "chaperone binding region" in claim 45 includes a peptide sequence that is capable of binding to any intracellular protein.

The instant specification does not define the limitation "wholly or partially unknown". Unknown is the opposite of known which means apprehended with certainty (wordnet.princeton.edu/perl/webwn). A target sequence may be known by some subjects and unknown by others. Thus, the term "unknown" may be interpreted with respect to different individuals. The specification does not define to whom the target sequence is unknown. Alternatively, unknown can be defined as in mathematics as a variable whose value is undetermined. Thus, the scope of the target binding region includes all possible peptide sequences regardless of whether or not they have been discovered, synthesized, isolated, characterized or designed.

Actual Reduction to Practice

The claimed invention was not reduced to practice at the time of filing.

Disclosure of Drawings or Structural Chemical Formulas

The specification does not include drawings or structural chemical formulas representing cyclic peptides that exemplify the claimed invention.

Relevant Identifying Characteristics

Complete structure: The specification does not present the complete structure of a single cyclic peptide of the instant invention.

Partial Structure: The specification states that the chaperone binding region may comprise Ala-Gly-Pro-Ile, for binding to the immunophilin cyclophilin A, or Leu-Pro, for

binding to the immunophilin FKBP12. These partial structures correspond to a very narrow subset of the genus chaperone binding region. The specification does not describe any other sequences that bind to cyclophilin A or FKBP12, present evidence to suggest that these sequences bind to any other intracellular protein or disclose any other sequence motif that binds to any other intracellular protein.

Physical and/or chemical properties: The specification does not describe the physical or chemical properties of the chaperone binding regions of the instant invention. Given the diversity of the genus of intracellular proteins and the complexity of their corresponding structures and solvent accessible surfaces, it would not be possible to establish a generic set of properties that could describe all peptides capable of binding to all proteins. Rather, the physical and chemical properties required for binding depends on the unique properties of the individual chaperone polypeptides. The specification fails to disclose this information for any chaperone, including the immunophilins cyclophilin A and FKBP12.

Structure/Function Correlation: The specification does not describe a correlation between the function of binding to an intracellular protein and the structure of a peptide ligand. The relationship between structure and function depends on the structure of the chaperone protein. The specification recites a number of polypeptides that could be used as a chaperone in the instant invention (Table 2) but does not describe a single peptide motif that is known to bind to any of the chaperones other than Ala-Gly-Pro-Ile, for binding to the immunophilin cyclophilin A, and Leu-Pro, for binding to the immunophilin FKBP12.

Method of Making the Claimed Compounds

Methods of making cyclic peptides and combinatorial libraries comprising cyclic peptides are known in the art and are described in the specification (paragraphs 0050-0060). Such methods could be used to make the cyclic peptides of the instant invention however the specification does not describe in structural terms what peptides fall within the genus. A method of screening a peptide library for sequence that bind to a chaperone polypeptide (paragraphs 0043-0045) does not constitute a method of making the chaperone binding region; it constitutes a method of discovering a chaperone binding region.

Level of Skill and Knowledge and Predictability in the Art

It is not within the skill of those in the art to design peptide ligands that specifically bind to polypeptides without significant experimentation. In their recent review of the field Ginalski *et al.* (*Nuc. Ac. Res.*, **2005**, *33*, 1874) write: "Currently available structure prediction methods do not allow for high-quality predictions of the quaternary structure of protein complexes and for the prediction of interactions between proteins. Current benchmarks indicate that methods predicting interactions can be successful mainly in case when structures exhibit minimal conformational changes upon complex formation. Substantial errors observed in predicted models go beyond the limits tolerated by such methods."

Conclusion

The scope of the genus cyclic peptides is immense, encompassing all peptides capable of binding to an intracellular polypeptide and an unknown or random sequence. Despite this scope, the specification fails to disclose a single species and presents only two partial sequences that may be incorporated into the chaperone binding region for binding to cyclophilin A and FKBP12. These species are of insufficient variety to reflect the vast scope of the entire claimed

genus which includes chaperones other than immunophilins. The claims are not limited to cyclic peptides that share a common structural core. Rather the cyclic peptides are claimed only in functional terms, an ability to bind to any intracellular polypeptide. The functional language of the claims is not supported by a structure-function correlation in the specification, nor is it within the ordinary skill of the art to predict the structure of a peptide that binds to a representative number of intracellular proteins, as evidenced by Ginalski *et al.* When the above factors are weighed, one of ordinary skill in the art would not recognize that Applicant was in possession of the claimed cyclic peptides at the time of filing.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 45-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 45 recites the limitation "a target binding region of wholly or partially unknown sequence." The specification fails to define this limitation in a way that clearly delineates the metes and bounds of the claim. First, the term "partially" is a relative term that is not defined in the specification in the context of a target sequence. That is, the specification does not define to what extent the target sequence may be known and fall within the scope of the claim. Second, the term "unknown" is vague and indefinite. Unknown is the opposite of known which means apprehended with certainty (wordnet.princeton.edu/perl/webwn). A target sequence may be known by some subjects and unknown by others. Thus, the term "unknown" may be interpreted with respect to different individuals. The specification does not define to

whom the target sequence is unknown. Alternatively, unknown can be defined as in mathematics as a variable whose value is undetermined. In the absence of a definition in the specification, the skilled artisan would not be able to discern the metes and bounds of the claim scope.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 45, 46 and 48-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Bashwira *et al.* (*Tetrahedron*, **1989**, *45*, 5845-5852). Claim 45 is drawn to a cyclic peptide, the sequence of which is defined only in functional terms. The cyclic peptide comprises two functional regions: a chaperone binding region and a target binding region. Claims 46 and 48-51 recite additional functional limitations. Claim 52 recites a structural limitation, namely that the chaperone-binding region comprise the sequence Ala-Gly-Pro-Ile or Leu-Pro. Bashwira *et al.* teach the cyclic peptide c(Ala-Gly-Pro-Ile-Val-Phe) isolated from *Clerodendrum myricoides* (abstract), which comprises the sequence Ala-Gly-Pro-Ile. Although Bashwira *et al.* do not specifically state that the cyclic peptide comprises a chaperone and target-binding region and that Ala-Gly-Pro-Ile has the function of binding to a chaperone or that Val-Phe has the function of binding to a target. However, the cyclic peptide taught by Bashwira *et al.* meets all of the

structural limitations of the claims, namely that it is a cyclic peptide consisting of Ala-Gly-Pro-Ile and an additional peptide sequence, the functional limitations are inherently met. See MPEP § 2112.01.

10. Claims 45, 46, 49-51, 53, 54 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Chakraborty *et al.* (*Current Biology*, **1995**, *2*, 157-61). Chakraborty *et al.* teach the design and synthesis of a hybrid molecule containing the rapamycin-FK506-ascomycin immunophilin-binding domain and a peptide tether (Figures 1 and 2) . Chakraborty *et al.* teach that the hybrid molecule, which is a cyclic peptide, exhibits powerful binding properties to the immunophilin FKBP12 but no activity in IL-6 dependent B-cell proliferation or in a IL-2 reporter assay (Biological Studies, pp. 158-159). Thus, the new molecule possesses the immunophilin-binding region of rapamycin, FK506 and ascomycin, but not their target-binding regions. In place of the target binding region is a peptide tether which completes the cyclic peptide.

Although Chakraborty *et al.* does not specifically state that the new cyclic peptide contain the target-binding region of FK506, it does contain a peptide tether of unknown function. Because the cyclic peptide taught by Chakraborty *et al.* meets all of the structural limitations of the claims, namely that it is a cyclic peptide consisting of a chaperone-binding region and an additional peptide sequence, the additional functional limitations regarding target binding are inherently met. See MPEP § 2112.01. With respect to claims 49-51 and 56, the chaperone-binding region binds to the immunophilin, FKB12, an FK-binding protein (Figures 1 and 2). With respect to claims 53, 54 and 56, Chakraborty *et al.* teach a method comprising

administering the cyclic peptide to a cell and assessing whether a phenotype of the cell has been altered (Biological Studies, pp. 158-159).

11. Claims 45, 46, 49-51, 53, 54 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu *et al.* (*Biochemistry*, **1992**, *31*, 3896-3901). Liu *et al.* teach analogues of cyclosporin A and FK506, cyclic peptides comprising a chaperone binding region and a target binding region (Figure 2 and Table II). The cyclosporin A and FK506 analogues comprise regions that bind to the chaperones cyclophilin A and FKPB12, respectively (Table I). The cyclosporin A and FK506 analogues also comprise regions that bind to the target calcineurin (Table II). The sequence of the target binding region in each analogue was unknown prior to conception by Liu *et al.* and therefore meets the limitations of claim 45. With respect to claim 46, the complex formed between the immunophilins cyclophilin A and FKB12 and their ligands cyclosporin A and FK506, serves to present the target binding region to calcineurin (p. 3897, col. 1). With respect to claim 48, the cyclosporin A and FK506 analogues bind to immunophilins (Table 1). With respect to claim 50, the cyclosporin A and FK506 analogues bind to cyclophilin and KK-binding protein, respectively. With respect to claim 51, the FK-binding protein is FKB12 (Table 1). With respect to claim 53, Liu *et al.* teach a method comprising a) administering the cyclosporin A and FK506 analogues to a cell; and b) assessing whether a phenotype of the cell has been altered (p. 3898, col. 1). Specifically, Liu *et al.* teach an assay for T-cell activation comprising the administration of the cyclosporin A and FK506 analogues to activated T lymphoblastoid cells transfected with an NF-AT-βGal construct; and the measurement of β-galactosidase activity to determine if signal transduction is inhibited (p. 3898, col. 1). With respect to claims 54 and 56, the cyclosporin A and FK506 analogues comprise

regions that bind to the chaperones cyclophilin A and FKPB12, respectively, which are endogenous proteins (Table I).

12. Claims 45, 46, 49, 50, 52-54 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Billich *et al.* (*J. Virology*, **1995**, *69*, 2451-2461). Billich *et al.* teach cyclosporin A analogues including [Leu^5Pro^6]Cs (Table 1). The cyclosporin A analogues are cyclic peptides comprising a chaperone binding region and a target binding region (Table I). The cyclosporin A analogues comprise regions that bind to the chaperone cyclophilin (Table I). The cyclosporin A analogues also comprise regions that bind to cellular proteins leading to immunosuppression (Table 1). The sequence of the target binding region in each analogue was unknown prior its original discovery and therefore meets the limitations of claim 45. With respect to claim 46, the complex formed between cyclophilin A and the cyclosporin A analogues, serves to present the target binding region to cellular proteins (p. 2452, col. 1). With respect to claims 49 and 50, the chaperone binding region binds to the immunophilin cyclophilin (Table 1). With respect to claim 52, the cyclic peptide comprises the sequence PL (Table I, compound XIII). With respect to claim 53, Billich *et al.* teach a method comprising a) administering the cyclosporin A analogues to a cell; and b) assessing whether a phenotype of the cell has been altered (p. 2453, col. 1). Specifically, Billich *et al.* teach an assay for T-cell activation comprising the administration of the cyclosporin A to activated T lymphoblastoid cells transfected with an NF-AT-βGal construct; and the measurement of β-galactosidase activity to determine if signal transduction is inhibited (p. 2453, col. 1). With respect to claims 54 and 56, the cyclosporin A analogues comprise regions that bind to the chaperone cyclophilin A, which is an endogenous protein (Table I).

13. Claims 45-48, 53-55 and 58 are rejected under 35 U.S.C. 102(e) as being anticipated by Kinsella (U.S. Patent No. 7,105,341. Kinsella teach a library (paragraph 0124) of cyclic peptides wherein each peptide comprises a random sequence (paragraph 0075) and a constant peptide sequence (paragraph 0105) capable of interacting with an intracellular protein selected from a glycosylation site, a compartmental retention sequence, a palmitoylation site, a nuclear localization sequence (Figure 8), a biotinylation recognition sequence (Figure 10) or an epitope (Figure 11). With respect to claim 45, the random sequence represents a target-binding region of unknown sequence. The glycosylation site, compartmental retention sequence, palmitoylation site, nuclear localization sequence (Figure 8), biotinylation recognition sequence (Figure 10) and epitope (Figure 11) represent the chaperone-binding region as defined in claim 45, that is, a region capable of with an intracellular peptide to form a complex (paragraphs 0105-0123)..

With respect to claim 46, Kinsella does not teach the complex presents the target binding region to other polypeptides in the cell. Because the cyclic peptides taught by Kinsella meet the structural limitations of the claim, this additional functional limitation is inherently met according to MPEP § 2112.01.

With respect to claim 47, the target binding sequence is a random peptide sequence (paragraphs 0059-0060). Specifically, Kinsella teach that the synthetic process can be designed to generate randomized proteins to allow the formation of all or most of the possible combinations over the length of the sequence, thus forming a library of randomized peptides (paragraph 0075).

With respect to claim 48, the cyclic peptide is genetically encoded in a retroviral DNA, intein-mediated system. Specifically, Kinsella teach methods for generating libraries of cyclic

peptides using inteins. Inteins are self-splicing proteins that occur as in-frame insertions in specific host proteins. In a self-splicing reaction, inteins excise themselves from a precursor protein, while the flanking regions, the exteins, become joined via a new peptide bond to form a linear protein. By changing the N to C terminal orientation of the intein segments, the ends of the extein join, forming a cyclized extein. Kinsella teach that because intein function is not strongly influenced by the nature of the extein polypeptide sequences located between them, standard recombinant methods can be used to insert random libraries into this position. Placement of these intein libraries into any number of delivery systems allows for the subsequent expression of unique cyclic peptides within individual cells. Such cells can then be screened to identify peptides of interest. (paragraphs 0059-0060, 0126-0140).

With respect to claim 53, Kinsella teaches a method of administering the cyclic peptides to a cell and assessing whether a phenotype of the cell has been altered (paragraph 0173).

With respect to claim 54, the cell may comprise an endogenous intracellular domain to which said chaperone binding region binds such as in the case of the glycosylation site, compartmental retention sequence, palmitoylation site, and nuclear localization sequence (Figure 8).

With respect to claim 55, the cell may comprise an exogenous intracellular domain to which said chaperone binding region binds such as in the case of a yeast two-hybrid assay involving the biotinylation recognition sequence (Figure 10) or the epitope (Figure 11).

With respect to claim 57, the cyclic peptide is administered to a cell as a polynucleotide capable of expression said cyclic peptide in said cell, specifically a retroviral DNA encoding an intein system (paragraphs 0126-0140 and 0173).

With respect to claim 58, Kinsella teach a method for determining the sequence of the target binding region of a cyclic peptide that alters the phenotype of a cell (paragraphs 0192-0196).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 45-51, 53, 54 and 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakraborty *et al.* (*Current Biology*, **1995**, *2*, 157-61) in view of Huffman *et al.* (U.S. Patent No. 6,194,544).

Chakraborty *et al.* teach that rapamycin, ascomycin, FK506 and cyclosporin are naturally-occurring substances with potent immunosuppressive properties. These compounds bind tightly to the immunophilins, a class of cytosolic proteins, forming complexes which in turn serve as ligands for other cellular targets involved in signal transduction. Cyclosporin binds to cyclophilin, while ascomycin, FK506 and rapamycin all bind to FKBP12. The target of the cyclophilin-cyclosporin, FKBP12-ascomycin and FKBP12-FK506 complexes is calcineurin whereas that of FKBP12-rapamycin complex is FRAP. Chakraborty *et al.* teach that the structures of FKBP12 and its ligands, FK506, ascomycin and rapamycin have been elucidated by NMR spectroscopy and X-ray crystallography. Together with extensive biological results, these studies established that each of these novel immunosuppressants bears two distinct domains, one that binds to the immunophilin receptor and another that together with the immunophilin, binds

to a second protein target. Thus, binding to the immunophilin via the binding domain creates a new binding surface comprised of the target domain on the immunosuppressant and a surface on the immunophilin that in turn binds to a target protein, exerting a specific biological action. (Introduction, p. 157).

Chakraborty *et al.* teach the design and synthesis of a hybrid molecule containing the rapamycin-FK506-ascomycin immunophilin binding domain and a peptide tether (Figures 1 and 2) . Chakraborty *et al.* teach that the hybrid molecule, which is a cyclic peptide, exhibits powerful binding properties to the immunophilin FKBP12 but no activity in IL-6 dependent B-cell proliferation or in a IL-2 reporter assay (Biological Studies, pp. 158-159). Thus, the new molecule possesses the immunophilin-binding region of rapamycin, FK506 and ascomycin, but not their target-binding regions. In place of the target binding region is a peptide tether which completes the cyclic peptide.

Chakraborty *et al.* teach that the "structure of our designed FKBP-binding compound is modular. It is therefore now practical to generate a large number of these compounds, with or without the addition of domains that mimic the" naturally occurring target-binding domains. "It is conceivable that molecules may emerge from such libraries of related compounds that mimic or antagonize the biological action of rapamycin or FK506/ascomycin, or even both. Such compounds may find useful applications in biology as tools, or in medicine as improved immunosuppressive agents." (p. 159, col. 2)

Chakraborty *et al.* do not teach the synthesis of a cyclic peptide library wherein each cyclic peptide comprises a immunophilin-binding domain based on rapamycin-FK506-ascomycin or cyclosporine A and a putative target-binding domain comprising a random

sequence. Chakraborty *et al.* teach the synthesis of a single cyclic peptide with the above properties but do not teach a combinatorial method for generating a library.

Huffman *et al.* teach a the synthesis of cyclic penta- and hexa-peptide libraries containing one or more known amino acids and one or more randomized amino acids, and methods for screening the library for new bioactive peptides and for elucidating structural information pertinent to drug design (abstract).

It would have been obvious to one of ordinary skill in the art to synthesize a cyclic peptide library wherein each cyclic peptide comprises a immunophilin-binding domain based on rapamycin-FK506-ascomycin or cyclosporin A, and a putative target-binding domain comprising a random sequence using the general synthetic scheme outlined in Huffman *et al.* Specifically the "known amino acids" in the method of Huffman *et al.* would be the immunophilin-binding domain of one of the immunosuppressant drugs of Chakraborty *et al.* and the random amino acids would be the target-binding region, satisfying claims 45-47 and 49-51. With respect to claim 48, the random sequence representing the target-binding region may consist of naturally occurring amino acids, which are genetically encoded in other contexts. The resulting peptide would have the same structure whether it is chemically synthesized or biologically expressed. Therefore, the limitation of claim 48 is met. It would have been further obvious to design an assay to screen the library for cyclic peptides that affect the phenotype of a cell, satisfying claims 53 and 56, and to determine the structure of the active cyclic peptide, satisfying claim 58. With respect to claims 54 and 55, the immunophilin could be endogenous or exogenous to the cell depending on the screening method utilized.

The skilled artisan would have been motivated to make such a library given that Chakraborty *et al.* establishes that it is possible to separate the immunophilin-binding and target-binding domains of the base immunosuppressant molecules and to create a new cyclic peptide possessing just one of the domains, the immunophilin-binding domain. Furthermore, Chakraborty *et al.* explicitly states that based on this result, it would be possible and desirable to generate a library of compounds wherein each compound comprises the immunophilin-binding domain as a constant region and a randomized or derivatized region that has the potential to bind to a target protein. By expanding the structure of the target region, the immunophilin-cyclic peptide complex could have expanded functional capabilities. Chakraborty *et al.* argue that such a library could yield "improved immunosuppressive agents." Chakraborty *et al.* further motivates the synthesis of the library stating that: "Immunosuppression is an important area of research, the medical benefits of which include the ability to transplant organs successfully and to treat a variety of immune diseases" (p. 159, col. 1). There would have been a reasonable expectation of success given that Huffman *et al.* teach a method of combinatorial cyclic peptide synthesis resulting in a library of compounds comprising constant and variable regions, as well as means for screening the library and determining the structure of active compounds. Furthermore, as evidenced by Chakraborty *et al.*, the structure-activity relationship of immunosuppressant-immunophilin binding is well-known in the art as are cell-based assays for immunosuppressant activity. This knowledge would guide the skilled artisan in the design and synthesis of the library and screening methods, as well as in the interpretation of results. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

16. Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chakraborty *et al.* (*Current Biology*, **1995**, *2*, 157-61), as applied to claims 45-51, 53, 54 and 56-58 above, in further view of Cochran *et al.* (US 2006/0110777) and Ivery (*Medicinal Research Reviews*, **2000**, *20*, 452-484). Chakraborty *et al.* motivate the synthesis of a combinatorial cyclic peptide library wherein each peptide comprises a immunophilin-binding region and a putative target-binding region (see rejection above). Chakraborty *et al.* do not teach that the immunophilin-binding region comprises Ala-Gly-Pro-Ile or Leu-Pro.

Cochran *et al.* teach that the phage display of cyclic peptide libraries has the following advantages: "This method allows the preparation of libraries as large as 10^{10}-10^{12} unique peptide members, many orders of magnitude larger than libraries that may be prepared synthetically. In addition to large library sizes, advantages of phage display include ease of library construction (Kunkel mutagenesis), coupling of the binding entity (displayed peptide) to a unique identifier (its DNA sequence), a selection protocol for amplifying rare binding clones in a pool, and the high fidelity of biosynthesis (compared to synthetic methods). Furthermore, rapid and inexpensive selection protocols are available for identifying those library members that bind to a target of interest." (paragraph 0009) Cochran *et al.* teach a method of generating a phage display cyclic peptide library (paragraph 0011).

In order to take advantage of the benefits of phage display as a means for generating a cyclic peptide library, the cyclic peptides in the library must be entirely encoded by DNA. The cyclic peptide of Chakraborty *et al.* in contrast is not genetically encoded and must be chemically synthesized. Specifically, the immunophilin-binding region of rapamycin-FK506-ascamycin in the cyclic peptide of Chakraborty *et al.* is chemically synthesized.

Ivery teaches that peptide comprising the sequence Ala-Gly-Pro-Ile and Leu-Pro bind tightly to cyclophilin A at the cyclosporin binding site (Figures 7 and 8, pp. 477-479, Table II). These peptides can be genetically encoded.

It would have been obvious to substitute the immunophilin-binding domain in the cyclic peptide taught by Chakraborty *et al.* with the peptides comprising either Ala-Gly-Pro-Ile or Leu-Pro taught by Ivery. The Ala-Gly-Pro-Ile and Leu-Pro peptide would serve the same function in the cyclic peptide, namely the region responsible for immunophilin binding. The peptide tether taught by Chakraborty *et al.* would be replaced with a random putative target binding sequence for the reasons discussed above. The skilled artisan would have been motivated to make this substitution because the resulting cyclic peptide could be entirely genetically encoded and thus synthesized as a phage display library according to the method of Cochran *et al.* and harboring the advantages recited above. There would have been a reasonable expectation of success given that Ivery report the high resolution structure of the peptide-cyclophilin interaction (Figures 7 and 8). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

17. Claims 52 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakraborty *et al.* (*Current Biology*, **1995**, *2*, 157-61), as applied to claims 45-51, 53, 54 and 56-58 above, in further view of Kinsella (U.S. Patent No. 7,105,341) and Ivery (*Medicinal Research Reviews*, **2000**, *20*, 452-484). Chakraborty *et al.* motivate the synthesis of a combinatorial cyclic peptide library wherein each peptide comprises a immunophilin-binding region and a putative target-binding region (see rejection above). Chakraborty *et al.* do not teach that the immunophilin-binding region comprises Ala-Gly-Pro-Ile or Leu-Pro.

Kinsella teach the use intein function, derived from wild-type or mutant intein structures, to generate cyclic peptide libraries *in vivo*. Methods are described for generating, identifying, and utilizing mutants with altered splicing/cyclization activity for use with cyclic peptide/protein libraries. Intein-generated cyclic libraries are described for the identification of cyclic peptides/proteins capable of altering a given cellular phenotype. Accordingly, it is an object of the invention to provide compositions and methods useful in the generation of random fusion polypeptide libraries *in vivo*. (Paragraph 0010)

In order to take advantage of the benefits of intein function as a means for generating a cyclic peptide library, namely the generation of the library *in vivo*, the cyclic peptides in the library must be entirely encoded by DNA. The cyclic peptide of Chakraborty *et al.* in contrast is not genetically encoded and must be chemically synthesized. Specifically, the immunophilin-binding region of rapamycin-FK506-ascamycin in the cyclic peptide of Chakraborty *et al.* is chemically synthesized.

Ivery teaches that peptide comprising the sequence Ala-Gly-Pro-Ile and Leu-Pro bind tightly to cyclophilin A at the cyclosporin binding site (Figures 7 and 8, pp. 477-479, Table II). These peptides can be genetically encoded.

It would have been obvious to substitute the immunophilin-binding domain in the cyclic peptide taught by Chakraborty *et al.* with the peptides comprising either Ala-Gly-Pro-Ile or Leu-Pro taught by Ivery. The Ala-Gly-Pro-Ile and Leu-Pro peptide would serve the same function in the cyclic peptide, namely the region responsible for immunophilin binding. The peptide tether taught by Chakraborty *et al.* would be replaced with a random putative target binding sequence for the reasons discussed above. The skilled artisan would have been motivated to make this

substitution because the resulting cyclic peptide could be entirely genetically encoded and thus synthesized *in vivo* using the retroviral DNA encoded intein method taught by Kinsella, thus satisfying claims 52 and 57. There would have been a reasonable expectation of success given that Ivery report the high resolution structure of the peptide-cyclophilin interaction (Figures 7 and 8). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

20. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

21. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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